REMARKS

Reconsideration and withdrawal of the rejections of this application are respectfully requested.

I. Status of Claims and Formal Matters

Claims 1, 7-9,14,15 and 19-30 are under examination in this application. Claims 1, 9, 15, 23 and 27 are currently amended and claim 30 is cancelled.

Support for the amended claims and new claims can be found throughout the application. No new matter is added. It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. The Rejections Under 35 U.S.C. §103 Are Overcome

Claims 1, 9, 14, 15, 19-23, 26, 27 and 30 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gervitz *et al.* (U.S. Patent No. 5,635,204; hereinafter "Gervitz") in view of both Mayer *et al.* (U.S. Patent No. 5,635,204; hereinafter "Mayer") and Caruso *et al.* (U.S. Patent No. 5,891,885; hereinafter "Caruso"). It is alleged that the combination of Gervitz and Mayer renders obvious a composition comprising morphine, ketamine and an excipient and further, that the combination of Gervitz, Mayer and Caruso would render obvious such a composition for topical use or formulation. Applicants respectfully disagree and traverse the rejection.

It is respectfully asserted that the cited references, taken either alone or in combination fail to teach or suggest a composition comprising morphine, ketamine and an excipient for exclusive use in the periphery.

Gervitz and Caruso are alleged to teach compositions for topical administration, however, Gervitz and Caruso are not alleged to teach compositions for topical use that is exclusive to the periphery and in fact, do not teach compositions for topical use that is exclusive to the periphery. The compositions of Gervitz and Caruso, including the topical compositions, are solely intended for systemic formulation and administration.

Gervitz involves a method of administering surgical or general anesthesia in a mammal by providing a transdermal combination of fentanyl, a α_2-adrenergic agonist and an amnesia inducing drug. *See* Gervitz, column 1 lines 30-35 (stating "It has been discovered that by simultaneously administering particular combinations of drugs at particular dosage levels by means of a transdermal delivery system, the surgical stage of anesthesia may be induced in patients requiring such treatment.") and column 2, lines 8-19. Although topical methods of administration are contemplated in Gervitz, they do not include methods of administration for exclusive use in the periphery. Rather, the topical methods taught by Gervitz intend systemic administration via transdermal patches in order to achieve surgical or general levels of anesthesia. Effective plasma levels of amnesia inducing drugs and transdermal patches for delivering plasma levels of amnesia inducing drugs are described in Gervitz, as are the physiologic effects associated with systemic dosing. *See* Gervitz, column 2 lines 60-63 (stating that "[t]he initial action of the scopolamine induces a mild tachycardia which will be compensated for by the bradycardia that is induced by fentanyl and clonidine"), column 2 lines

66-67 to column 3 lines 1-4 and Example 2 (which states "[u]sing the procedure of Example 1, a transdermal patch containing clonidine is prepared which has sufficient clonidine to provide a plasma level of about 5 ng/ml.").

Caruso teaches methods and compositions for alleviating migraine headaches that include NMDA receptor antagonists. At column 5, lines 38-45, Caruso provides instructions for administration as follows:

> With regard to dosage levels, the antimigraine drug must be present in a migraine-treating amount, e.g., at a level corresponding to the generally recommended adult human dosages for the antimigraine drug, and the NMDA receptor blocker or substance that blocks a major intracellular consequence of NMDA activation must be present at a level that potentiates the migraine-treating effectiveness of the antimigraine drug.

Migraine pain derives from blood vessels beneath the skin. It is well known in the art that migraine medications are provided by systemic administration in order to reach those blood vessels and adequately treat the disorder. Although topical methods of administration are contemplated by Caruso at column 6, lines 26-31, just like Gervitz, Caruso does not contemplate methods of administration for exclusive use in the periphery. The compositions of Caruso (including the brief reference to topical compositions) are all intended to achieve the necessary systemic effect for migraine treatment.

It is alleged that the combination of Gervitz and Mayer renders obvious a composition comprising morphine, ketamine and an excipient and further, that the combination of Gervitz, Mayer and Caruso would render obvious such a composition for topical use or formulation because there would be an expectation of success in administering such a composition. It is additionally alleged that the combination of Gervitz, Mayer, Caruso and Mackles would render obvious a similar composition also comprising lidocaine. Much to the contrary, at the time the application for the present invention was filed, analgesic results achieved by systemic administration did not provide any expectation of success in achieving analogous results exclusively in the periphery.

At the time the application for the present invention was filed, the contribution of peripheral mechanisms to the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated systemically through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at

peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and NMDA receptor antagonists at these peripheral sites. In fact, several medical reports published before the filing of the present application teach that morphine fails to stimulate peripheral sites (all documents referred to herein are supplied on the Information Disclosure Statement accompanying this response).[1] Thus, the effectiveness morphine, much less tolerance attenuated doses of morphine, in the periphery is unexpected given the state of the art.

---

[1] *See* Raja SN, Dickstein RE, Johnson CA. (1992) "Comparison of Postoperative Analgesic Effects of Intraarticular Bupivacaine and Morphine Following Arthroscopic Knee Surgery," Anesthesiology 77:1143-7. Raja et al. describe a randomized, double-blinded study comparing the analgesic efficacy of bupivacaine and morphine administered intraarticularly in 47 patients having undergone arthroscopic knee surgery. The analgesic efficacy of the treatments were determined up to 72 hours following surgery by postoperative pain scores (VAS) and the amount of supplemental opioid required by each patient. A first group of patients received 20 ml of normal saline with 100 μg epinephrine. A second group received 20 ml of 0.25% bupivacaine and 100 μg of epinephrine. A third group received 3 mg of morphine and 100 μg of epinephrine in 20 ml of normal saline (15% morphine). All medicaments were administered by injection into the joint space of the knee via an 18-G needle following arthroscopic surgery. Raja et al. did not find any analgesic effect and/or activation of opioid receptors in the periphery as a result of intra-articular morphine administration. For example, the authors state on page 1146 that their study "fails to demonstrate functional opiate receptors in the knee joint in a clinical model of acute injury." Further, the authors conclude on page 1146 "that no evidence for a peripheral opiate-receptor mediated analgesia could be demonstrated in patients undergoing arthroscopic knee surgery under epidural anesthesia."

See also Rosenstock C, Andersen G, Antonsen K, Rasmussen H, Lund C. (1996) "Analgesic Effect of Incisional Morphine Following Inguinal Herniotomy Under Spinal Anesthesia," Reg. Anesth. 21:93-8. Rosenstock et al. describe a double-blind, randomized, placebo-controlled study to evaluate the possible immediate and long-term analgesic effect of morphine injected incisionally in patients undergoing minor abdominal surgery (inguinal herniotomy). Following surgery, the patients were divided randomly into one of four groups. The first group received 5 mg of morphine (in 6 ml of saline; 83% w/v) infiltrated in the edges of the surgical wound. The second group received 5 mg of morphine (in 6 ml of saline; 83% w/v) injected in the subcutaneous layer of the surgical wound. The third group received 5 mg of morphine intravenously. The fourth group (placebo) had 6 ml of saline injected in the edges of the surgical wound. Any resulting analgesia was assessed with visual analog scale (VAS) scores over the course of 7 days following the operation. Further, the dosage and frequency of supplemental analgesics (acetaminophen and morphine) required by each patient was considered. However, Rosenstock et al. did not find any difference in analgesic effect among the four groups. That is, the placebo group (group 4) provides statistically the same level of analgesia as the three groups having been administered morphine. Similarly, the results did not show any statistical differences between the group in VAS scores nor did the groups show any statistical difference in the postoperative consumption of acetaminophen, alfentanil, or fentanyl. The authors conclude on page 96 that "neither an immediate nor delayed postoperative analgesic effect of incisional morphine could be demonstrated..." in the study.

See also Picard PR, Tramer MR, McQuay HJ, Moore RA. (1997) "Analgesic Effect of Peripheral Opioids (all except intra-articular): A Qualitative Systematic Review of Randomised Controlled Trials" Pain 72:309-18. Picard et al. reviewed 26 randomized controlled trials ("RCT") carried out from 1987 through 1996 each directed at understanding whether an analgesic effect could be attained through activation of peripheral opioid receptors. In total, the 26 RCTs studied 925 patients, of which 485 received an opioid, including morphine, fentanyl, alfentanil, buprenorphine and butorphanol. The efficacy of the peripherally-applied analgesics was tested using a variety of surgical methods and analgesic administration methods, including intrapleural, intraperitoneal, incisional, and dental injections, perineural blocks, and brachial plexus sheath injections.
In reviewing the results and conclusions reached by the primary authors of each study to assess the evidence for peripheral opioid analgesia, the current authors conclude in the abstract that none of the studies provided "evidence

for a clinically relevant peripheral analgesic efficacy of opioids in acute pain." The current authors argue that the results of the 26 RCTs reviewed were either unequivocally negative (i.e., lacking support for peripheral opioid analgesia) or that the results were not clinically relevant. The current authors further state on page 316 that the primary authors "tended to over-interpret their findings and to confuse statistical significance with clinical relevance. In attentive or uncritical readers [of the studies] may be misled into a false perception of treatment efficacy." Further, the current authors conclude on page 316 that the "clinical use of peripheral opioids requires much more evidence than we have at present."

See also Yarussi A et al. (1999) "Evaluation of Peripheral Morphine Anlagesia for Lumpectomy and Axillary Node Dissection: A Randomized, Double-blind, Placebo-controlled Study," Reg. Anesth. Pain. Med. 24:142-5. Yarussi et al. describe a study to evaluate the post-operative analgesic effects, if any, of incisionally-administered morphine in patients undergoing lumpectomies and axillary node dissections in the treatment of breast cancer. The study was carried out in a double-blinded, placebo-controlled fashion and involved 45 patients. Prior to surgery, each patient was put under general anesthesia. The patients were then randomized into 3 groups: a first group wherein the surgical site was irrigated for 5 minutes with a 6% solution of morphine sulphate (6 mg in 100 ml of buffer); a second group wherein the 6% solution of morphine sulphate (6 mg in 100 ml of buffer) was administered by intramuscular injection; and a third group wherein the surgical site was irrigated with a placebo (100 ml of buffer) for 5 minutes. Analgesia was assessed by using a visual analog scale card (VAS), supplemental opioid (e.g. fentanyl) consumption, and incidences of side-effects. The authors did not detect any analgesic effect in any morphine-administered group relative to the placebo group. The authors conclude on page 144 that they are "unable to demonstrate any analgesic benefits after topical administration of morphine [at the surgical site]."

See also Moore UJ, Seymour RA, Gilroy J, Rawlins MD. (1994) "The Efficacy of Locally Applied Morphine In Post-Operative Pain After Bilateral Third Molar Surgery," Br. J. Clin. Pharmacol. 37:227-30. Moore et al., describe two consecutive studies on twenty patients to test the possibility of attaining opioid-induced analgesia through the activation of opioid receptors at peripheral sites of molar tooth sockets following the bilateral removal of the third molars. For each patient, the third molars were surgically removed a month apart. After the first surgery, a morphine gel was topically administered to the tooth socket having morphine at a concentration of either 100 ng/ml (0.01% w/v per 300 ul gel volume) or 100 ug/ml (10% w/v per 300 ul gel volume). After the second surgery, a placebo gel was administered to the tooth socket. Administration of the medicaments was carried out in a double-blind fashion. The overall level of analgesia provided by the morphine gel was assessed by patient-administered visual analogue scales (VAS) and by the dosage and frequency of escape analgesia requested by each patient. The results obtained do not show an antinociceptive response at peripheral sites following topical administration of morphine in the tooth socket. For example, on page 228 of Moore et al., the authors indicate that there is "no significant difference...between both locally applied morphine treatments and placebo." In other words, the data did not demonstrate any analgesic effect upon topical administration of morphine at the periphery (tooth socket) over and above the effect provided by the placebo. The authors further state that the results show "no clear efficacy in the control of postoperative pain after third molar surgery. Any 'peripheral activity' that morphine may exhibit does not thus appear to result in any antinociceptive effect..." The authors conclude that that no antinociceptive response to topical morphine administration is achieved at peripheral sites.

See also Roy and Flynn, (1989) "Transdermal Delivery of Narcotic Analgesics: Comparative Permeabilities of Narcotic Analgesics Through Human Cadaver Skin" Pharm. Research. 6:825-832. Roy and Flynn describe a study comparing absorption properties of six narcotic compounds and/or analgesics, including morphine. In this study, absorption is assessed by measuring the permeability coefficients of each drug on skin derived from human cadavers. Both acidic and free base forms of the drugs are tested. The study was carried out by obtaining skin from 48-hour human cadavers, which was then subjected to a skin permeation assay to test whether the compounds were able to pass through the skin mounted between two half-cells of a diffusion well apparatus. The results show that morphine (0.072% w/v in 250 µl), codeine and hydromorphone have low permeability coefficients (i.e., are poorly absorbed), which corresponds to their lower hydrophobicity and greater lipophilicity. The authors conclude that morphine, as well as other opioids, are not efficiently absorbed through human skin. For example, the authors state on page 831 that, "as a group, these [opioids] appear totally unsuited for transdermal delivery..." As observed by the authors, a topical composition is clinically inadequate due to lack of bioavailability when absorption is delayed to this extent. Thus, the conclusion in Roy et al. teaches the failure of a topical, antinociceptive composition comprising morphine.

See also Roy SD, Hou S-YE, Witham SL and Flynn, GL (1994) "Transdermal Delivery of Narcotic Analgesics: Comparative Permeabilities of Narcotic Analgesics Through Human Cadaver Skin and Hairless Mouse

For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). There must also be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993).

At the time the application for the present invention was filed, there was no reasonable expectation of success in practicing the claimed invention. As documented herein above, the successful application of the claimed invention for providing tolerance attenuated doses of morphine to the periphery was unexpected given the state of the art. The combination of Gervitz, Mayer and Caruso or Gervitz, Mayer, Caruso and Mackles provide solely for induction of systemic analgesia and do nothing to overcome the presumption in the art that use of opioids such as morphine in the periphery are comparatively much less effective. Thus, nothing in the cited references would provide the skilled artisan with an expectation of success in practicing the claimed invention, as it is limited to compositions and methods for use in the periphery.

Furthermore, systemic uses of opioids are non-analogous art, having no bearing on the function of topical compositions providing only localized effects in the periphery. Thus, reference to the amounts of fentanyl and ketamine contained in the systemic compositions of Gervitz on page 3 of the Office Action are likewise non-analogous because it is well known in the pharmaceutical arts that far less amounts of active agent are required to trigger a systemic effect than a peripheral effect. Differences associated with systemic and peripheral action are amplified with respect to the present invention, where opioids such as morphine comprise the active agent and effects in the periphery were considered to be suspect. Accordingly, the skilled artisan working to develop a localized peripheral pain reliever and methods of its use is not motivated by literature describing systemic analgesics, which would include the combination of Gervitz, Mayer and Caruso. Citation on the basis of non-analogous art is improper and should be

---

Skin" J. Pharm. Sciences 83:1723-1726. Roy et al describe a study in which the permeability of morphine to skin was further evaluated. The results showed that morphine (4% w/v in 250µl) was relatively impermeable to skin, as determined by both a human cadaver skin model and a mouse skin model. For example, the authors stated on page 1724 that the permeability coefficients of other drugs studied are "several orders of magnitude higher than those found for morphine hydrochloride..." In other words, the bioavailability of topical morphine was much lower than that of the other drugs in the study.

withdrawn. *In re Oetiker*, 977 F.2d 1443, 1446, 24 U.S.P.Q.2d 1443,1445 (Fed.Cir.1992). *In re Deminski*,796 F.2d 436, 230 U.S.P.Q. 313 (Fed.Cir.1986); *In re Clay*, 966 F.2d 656, 659, 23 U.S.P.Q.2d 1058,1060-61 (Fed.Cir.1992).

Thus, there is no motivation for the skilled artisan to look to the teachings of Gervitz, Mayer, Caruso and Mackles, much less modify the teachings of the same to localize and manage opioid analgesia in the periphery. As stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." In the present Office Action, the art is only modified as suggested by the Examiner, as Gervitz, Mayer, Caruso and Mackles fail to provide any indication of desirability of making such modifications to provide analgesia selectively to the periphery. *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992).

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103 are requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the amendments and remarks herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 04-1105.

Respectfully submitted,

Amy Leahy, Reg. No. 47,739
Edwards & Angell, LLP
Three Stamford Plaza
301 Tresser Blvd., 6th Floor
Stamford, CT 06901
Tel. No. (203) 353-6836

Date: April 11, 2005